REMARKS

Applicants respectfully request reconsideration and allowance of all pending claims.

I. Status of the Claims

In this Amendment B, claims 1, 3, 4, 5, 7, 12, 13, 14, 24 and 25 have been amended to more particularly claim certain preferred embodiments, and/or to ensure proper antecedent basis is present therein. Additionally, claim 2 has been canceled. Accordingly, claims 1 and 3-25 are now pending.

With respect to claim 1, it is to be noted that this claim has been amend to call for (i) the impure preparation referenced therein to comprise fentanyl containing phenethylpiperaniline, (ii) the pure fentanyl to comprise a phenethylpiperaniline impurity level of less than 0.010 weight percent, and (iii) a loading ratio of column media to fentanyl in the range of from about 50 to about 150. Support for these amendments can be found in originally filed claims 2 and 24, as well as in the instant specification at paragraphs [0014]-[0015] and [0029].

II. 35 U.S.C. 112, second paragraph

Reconsideration is requested of the rejection of claims 1, 3, 9, 19, 20, and 22-25 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1

Claim 1 has been rejected as reciting "highly pure" without distinctly stating what high purity means. Applicants have amended claim 1 to remove the phrase "highly pure" and replace it with the phrase "pure fentanyl compris[ing] a phenethylpiperaniline impurity level of less than 0.010 weight percent." Support for this amendment can be found in originally filed claim 24 and in the instant specification in paragraph [0015]. Accordingly, Applicants request that this rejection be withdrawn.

B. Claims 3, 9, 19, 20, and 22-24

Claims 3, 9, 19, 20, and 22-24 have been rejected as containing the term "about," which renders the metes and bounds of the claims vague and unclear. Applicants respectfully disagree, as one of ordinary skill in the art would reasonably be apprised of the scope of the invention in light of the specification despite the use of "about." Furthermore, Applicants call the Office's attention to MPEP 2173.05(b), which states:

> "[t]he fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification."

This section of the MPEP also states that "in determining the range encompassed by the term 'about', one must consider the context of the term as it is used in the specification and claims of the application."[1]

In the instant specification, both broad and narrow ranges are provided for various parameters including, for example, the loading ratio as required in claims 1 and 3 (see the specification at, for example, paragraphs [0029] and [0033]). Additionally, the working Examples teach various load ratios, so as to provide one skilled in the art with guidance as to what is meant by "about". Accordingly, Applicants respectfully submit that the rejection of claims 3, 9, 19, 20, and 22-24 should be withdrawn.

C. Claim 25

Claim 25 has been rejected as containing the term "substantially," which is said to render the metes and bounds of the claim vague and unclear. Applicants have amended claim 25 to remove "substantially" from the claim. Accordingly, the rejection of claim 25 should be withdrawn.

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1 MPEP 2173.05(b), quoting Ortho-McNeil Pharm. Inc. v. Caraco Pharm. Labs., Ltd., 476 F.3d 1321, 1326, 81 USPQ2d 1427, 1432 (Fed. Cir. 2007).

III. 35 U.S.C. 112, first paragraph

Reconsideration is requested of the rejection of claims 1 and 3-25 because, while the specification is enabling for one set of conditions for the purification of fentanyl, the specification does not reasonably provide enablement for the wide variety of reverse-phase high performance preparative liquid chromatography ("rphplc") conditions claimed; that is, reconsideration is requested of the rejection of these claims based on the Office's position that, because of the limited working Examples and the academic nature of discussions about rphplc in the specification, one of ordinary skill in the art would be faced with an undue amount of experimentation to use the invention to the full scope of the claims. Applicants respectfully disagree with the Office's position here.

A. Enablement Requirement

It is to be noted that, in order to satisfy the enablement requirement, the specification need only disclose sufficient information to enable one of ordinary skill in the art to make and use the invention without undue experimentation. (*See* MPEP §2164.01.) The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. (Id.)

B. *In re Wands*

(i) Nature of Invention / Breadth of the Claims

The Office asserts that the claims are drawn to generically "impure preparations" of fentanyl, and that the generic methods are claimed to be available for industrial processes, meaning large scale purification for all "impure preparations." Furthermore, the Office asserts that the list of stationary phases includes silicon based supports, neutral supports, basic supports, and acidic supports, rendering the breadth of the claims wide.

In response to the Office's assertions, Applicants respectfully point out that the rejected independent claims (i.e., claims 1 and 24) do not encompass all impure preparations. Specifically, the independent claims are directed to processes for recovering pure fentanyl (i.e., fentanyl comprising a phenethylpiperaniline impurity level of less than 0.010 weight percent) from an impure preparation comprising fentanyl

containing phenethylpiperaniline. Furthermore, the rejected independent claims do not encompass all processes using reverse-phase high performance preparative liquid chromatography; rather, these claims are directed to such a process for recovering pure fentanyl from the noted impure preparation wherein the loading ratio is in the range of from about 50 to about 150.

Additionally, it is to be noted that dependent claims 3-23 add further details to independent claim 1, such as details relating to specific stationary phases (e.g., claims 4-6) and the mobile phase (e.g., claims 7-23).

(ii) Level of One of Ordinary Skill / State of the Prior Art

Applicants respectfully submit the level of one of ordinary skill in the art would be high, having experience with preparative liquid chromatography separation techniques, the types of separation media that may be used, and the types of eluents or mobile phases that may be used. Additionally, in general, preparative liquid chromatography is a well known and understood separation technique.

(iii) Amount of Direction Provided / Existence of Working Examples

Applicants respectfully submit the amount of direction provided by the present specification is significant. For example, details are provided about the pH and the concentration of fentanyl in the "impure preparation" (see, e.g., paragraph [0025]), the stationary phase type and size (see, e.g., paragraphs [0007] and [0026]), the column itself (see, e.g., paragraph [0027]), the mobile phase type, concentration and pH (see, e.g., paragraphs [0028] and [0031]), loading ratio (see, e.g., paragraph [0029]), and temperature during separation or use (see, e.g., paragraph [0032]). Furthermore, the working examples provide results to illustrate, among other things, the impact of varying loading ratios on the purity of the fentanyl recovered, as measured in terms of the phenethylpiperaniline present therein.

(iv) Undue Experimentation

With respect to the quantity of experimentation necessary, the Office asserts that there are various solid stationary phases, supports (i.e., media) and eluents, which would lead to an inordinate and laborious amount of testing to simulate the disclosure

provided in the present application for the broadly-claimed conditions used in the "rphplc" methods and arrive at an equivalent set of findings for other stationary phases and media. In response thereto, Applicants again point out that the claims are now directed to methods using stationary phases and media, at a loading ratio in the range of from about 50 to about 150, to recover pure fentanyl (i.e., fentanyl comprising a phenethylpiperaniline impurity of less than 0.010 weight percent) from an impure preparation comprising fentanyl containing phenethylpiperaniline. Thus, testing would only need to be performed using impure preparations comprising fentanyl containing phenethylpiperaniline, and a loading ratio within the recite range. Furthermore, those tests would be easily monitored and evaluated, by testing the concentration of phenethylpiperaniline in the collected samples or cuts.

The Office's assertion that working Example 2 provides a cautionary tone is noted. Specifically, the Office points out that with one Si-C8 ligand column the results presented in Tables I and II of the specification show variability with regards to yield that was not predicted, and, as such, optimization and validation of developed methods would require undue experimentation for all impure preparations and for the plethora of solid supports and eluents (i.e., stationary phases and media) claimed. In response thereto, Applicants again point out that the claims are not directed to all impure preparations. Rather, as noted above, these claims are directed to a process that uses the recited impure preparation (comprising fentanyl containing phenethylpiperaniline) and the recited loading ratio.

C. Conclusion

In view of the foregoing, Applicants respectfully submit that, while there may be some degree of unpredictability in the field and/or some degree of experimentation needed, one of ordinary skill in the art would be able to recover pure fentanyl using reverse-phase high performance preparative liquid chromatography as claimed without undue experimentation, once armed with the disclosure in the present application, as well as the knowledge already generally present in the prior art. Accordingly, Applicants submit the rejected claims do satisfy the requirements of 35 U.S.C. 112, first paragraph. Reconsideration of this rejection is therefore requested.

IV. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 1 and 3-25 under 35 U.S.C. §103 as being obvious in view of Hofstadter (U.S. Patent No. 4,317,903).[2]

A. The Claimed Subject Matter

The present application is generally directed to a novel industrial process for recovering pure fentanyl from an impure preparation of fentanyl containing phenethylpiperaniline. More particularly, as currently pending, the independent claims of the present application are directed to an industrial process for recovering pure fentanyl, which as defined in the claims includes a phenethylpiperaniline impurity level of less than 0.010 weight percent, from an impure preparation comprising fentanyl containing phenethylpiperaniline. The process comprises subjecting the impure preparation to a reverse-phase high performance preparative liquid column chromatography, wherein a loading ratio of column media to fentanyl loaded onto the column is in the range of from about 50 to about 150.[3]

As noted in the present application (see, e.g., paragraph [0015]), Applicants discovered the claimed process can be employed, for example, using a series of collected fractions, which may be partially recycled, to obtain a highly purified fentanyl in a high yield. Specifically, fentanyl is produced with phenethylpiperaniline impurity levels less than 0.010 weight percent in the purified product. Furthermore, Applicants discovered the present process is particularly advantageous as compared, for example, to analytical HPLC, which would require a loading ratio significantly higher than the range recited here (see, e.g., paragraph [0029]).

B. The Cited Art

Hofstetter discloses methods of using a reverse-phase high performance preparative liquid chromatography to obtain a highly pure preparation of the antibiotic

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2 Applicants note additional prior art is referenced, but not relied upon, on pages 6-7 of the present Office action. Applicants therefore will not address these references at this time. However, Applicants respectfully reserve the right to do so at a later date.

3 As noted on page 5 of the specification (paragraph [0019]), "loading ratio" is the weight ratio of the stationary phase to the fentanyl loaded thereon; that is, it is a weight ratio of column media to fentanyl.

lincomycin hydrochloride. The methods generally comprise a number of steps, including: (a) dissolving approximately 450 grams of the starting material (i.e., impure preparation of lincomycin A and lincomycin B) per liter of 30% aqueous methanol; (b) applying the solution to a chromatography column filled with 18 grams of C18 bonded phase silica gel per gram of starting material; (c) stripping the remaining lincomycin from the column with 1 bed volume of methanol; (d) concentrating the lincomycin-rich eluate to dryness; (e) crystallizing the lincomycin according to standard crystallization procedure; (f) re-chromatographing the lincomycin B-rich fraction according to the above procedure; (g) concentrating the eluate containing greater than 98% lincomycin B to dryness; and (h) re-dissolving the solids in 3 milliliters of methanol per gram of lincomycin B solids at 40°C and adjusting the pH with concentrated hydrochloric acid to 1.5. Notably, Hofstetter states that the weight ratio recited in step (b) is "near optimum"; that is, Hofstetter states that the weight ratio of silica gel (i.e., the column media) to lincomycin is "near optimum" at 18:1.

C. The Claimed Subject Matter is Not Obvious

In order for the Office to show a *prima facie* case of obviousness, M.P.E.P. §2142 requires a clear articulation of the reasons why the claimed invention would have been obvious. Specifically, to reject a claim based on this rationale, the Office must articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at each and every limitation of the claimed invention; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. Applicants respectfully submit the Office has failed to establish a *prima facie* case of obviousness because each and every element of the claims has not been disclosed or suggested by the cited reference, and/or because there is no motivation to modify the reference in order to achieve the claimed subject matter.

Applicant submits that nowhere in the cited reference is a process for producing pure fentanyl disclosed or suggested. In fact, Hofstetter does not even mention fentanyl; rather, Hofstetter discloses the recovery of lincomycin. Furthermore, nowhere does Hofstetter disclose or suggest a process for obtaining a "pure" product, wherein the concentration of the impurity of concern or interest (i.e., phenethylpiperaniline) therein is less than about 0.010 weight percent; rather, Hofstetter is only concerned with limiting the concentration of lincomycin B to less than about 0.5 weight percent, which is significantly higher (i.e., 50 times higher) than the limit recited in the present claims. Finally, nowhere in the cited reference is a loading ratio of column media to fentanyl (or, in Hofstetter's case, lincomycin) in the range of between about 50 and about 150 disclosed or suggested. In fact, Hofstetter's statement that the disclose ratio of 18:1, which is more than 2.5 times less than the recited minimum of "about 50", is "near optimum" arguable teaches away from the recited ratio.

In view of the foregoing, Applicants respectfully submit that the cited reference fails to disclose or suggest each and every limitation of the claims. Applicants additionally submit that there is simply no motivation to modify the cited reference in order to achieve the claimed subject matter, because Hofstetter teaches away from the recited loading ratio. Applicants therefore submit the present rejection is improper, and accordingly request reconsideration and allowance of all pending claims.

V. Double Patenting Rejection

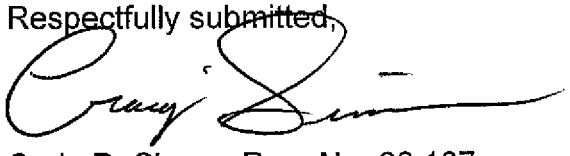
Applicants note that all pending claims have been rejected on the ground of nonstatutory obviousness-type double patenting in view of the pending claims of copending U.S. Patent Application Serial Nos. 10/501,353, 11/576,059, and 11/916,036. Applicants further note, however, that this rejection is a provisional obviousness-type double patenting rejection, since the applications have not yet issued as patents. Accordingly, Applicants respectfully reserve the right to address the merits of this rejection, as appropriate, if the listed applications issue as patents before the application at hand.

CONCLUSION

In view of the foregoing, Applicants respectfully request favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Amendment B in Response to Non-final Office Action.

Respectfully submitted,



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